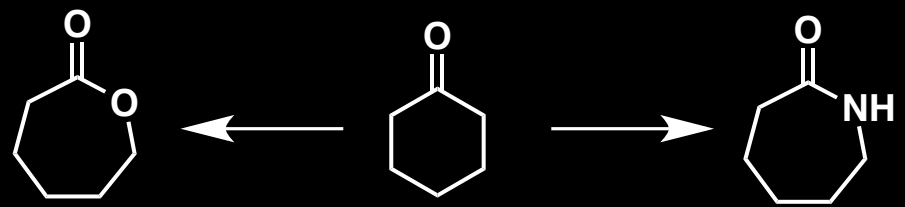
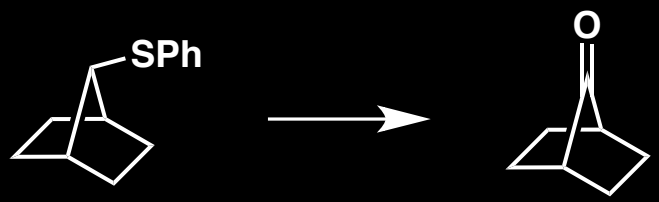
Rearrangement Reactions

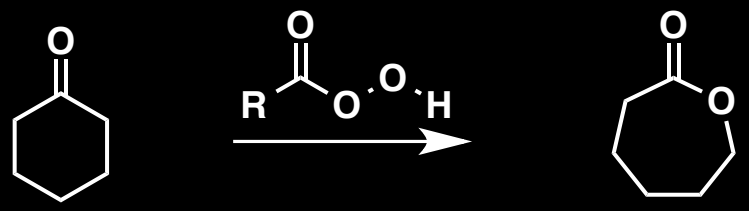
Lecture Notes





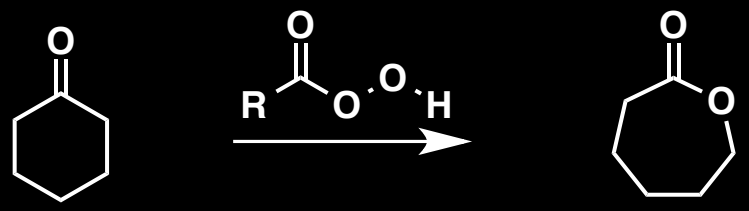
See slides for key review articles

The Baeyer-Villager Oxidation/Rearrangement

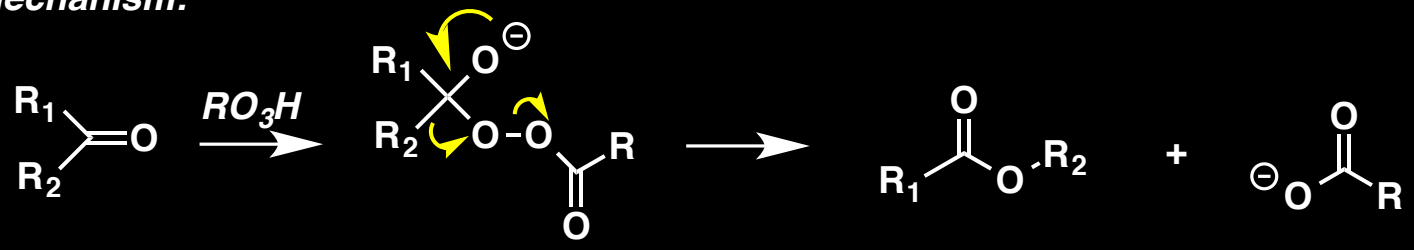


For a review, see: M. Renz, B. Meunier, Eur. J. Org. Chem. 1999, 737.

The Baeyer-Villager Oxidation/Rearrangement



Mechanism:



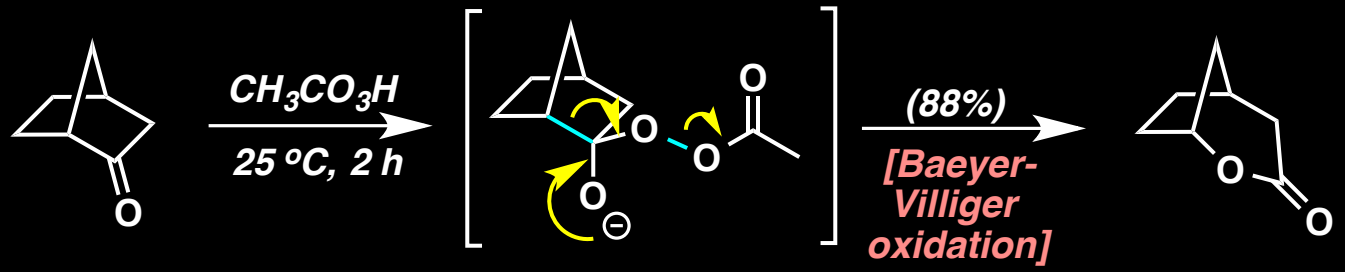
Criegee intermediate

Alkyl group that migrates does so with retention of configuration

More electron-rich (most substituted) alkyl group migrates in preference

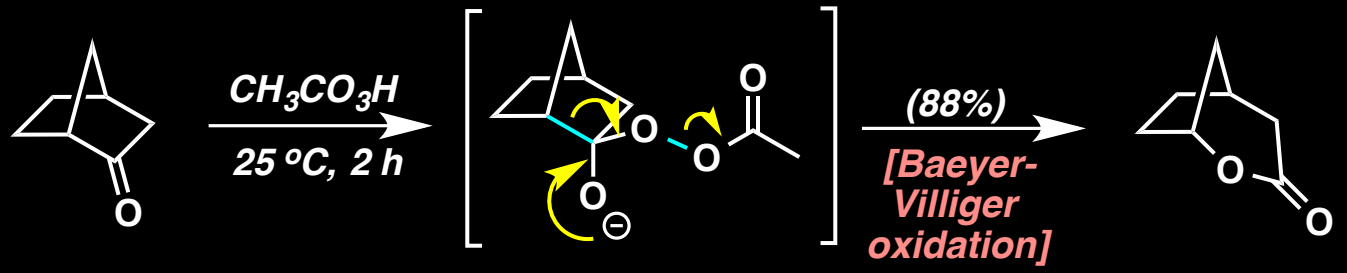
For a review, see: M. Renz, B. Meunier, Eur. J. Org. Chem. 1999, 737.

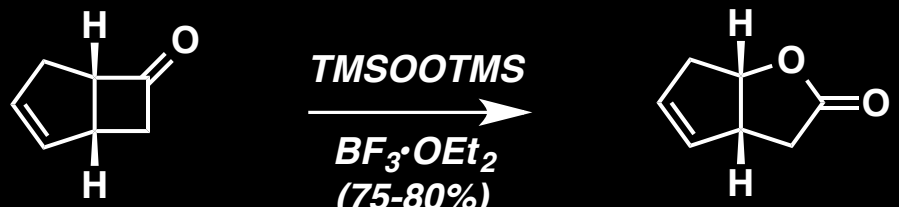
The Baeyer-Villager Oxidation/Rearrangement



J. Meinwald and co-workers, J. Am. Chem. Soc. 1960, 82, 5235.
R. Noyori and co-workers, J. Org. Chem. 1982, 47, 902.

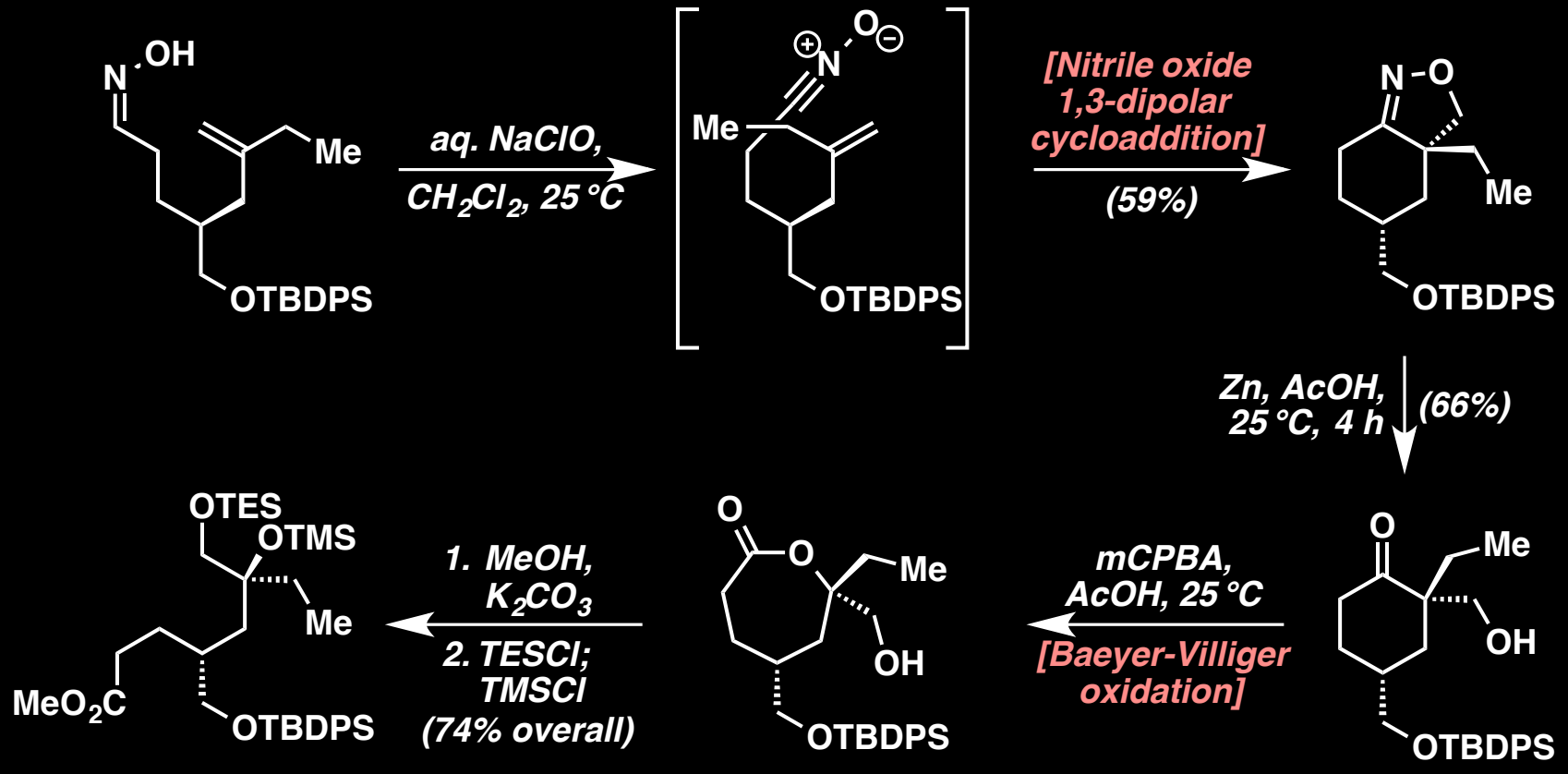
The Baeyer-Villager Oxidation/Rearrangement





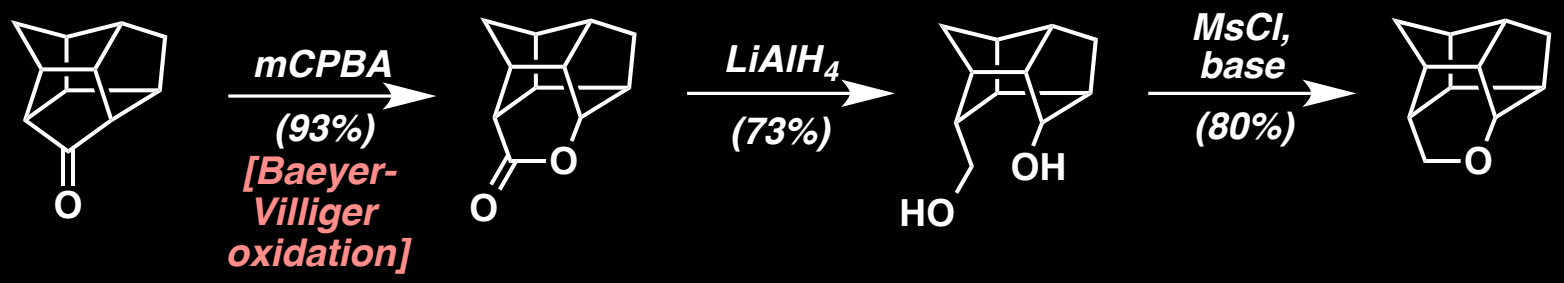
J. Meinwald and co-workers, J. Am. Chem. Soc. 1960, 82, 5235.
R. Noyori and co-workers, J. Org. Chem. 1982, 47, 902.

The Baeyer-Villager Oxidation/Rearrangement



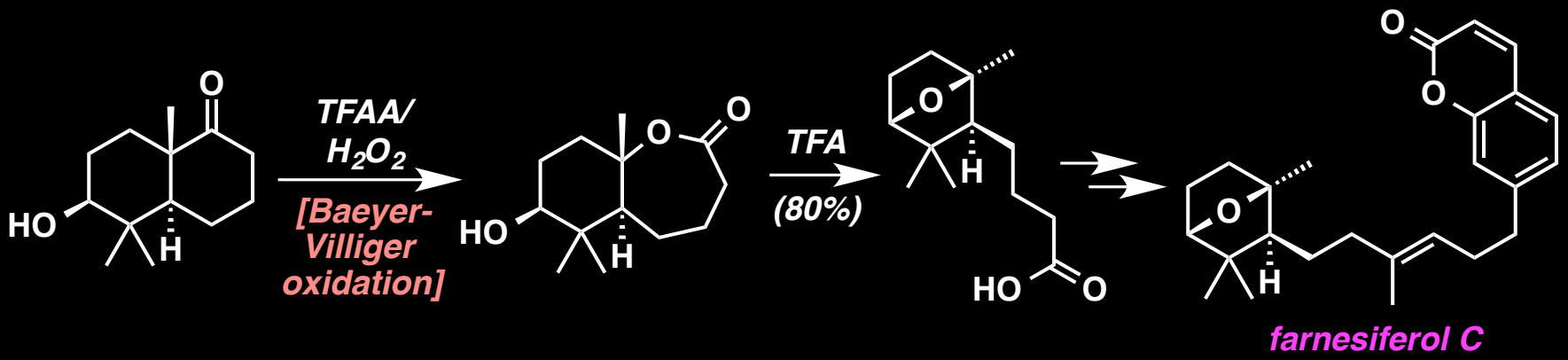
T. Fukuyama and co-workers, J. Am. Chem. Soc. 1999, 121, 3791.
For a review, see Classics in Total Synthesis II, Chapter 18.

The Baeyer-Villager Oxidation/Rearrangement



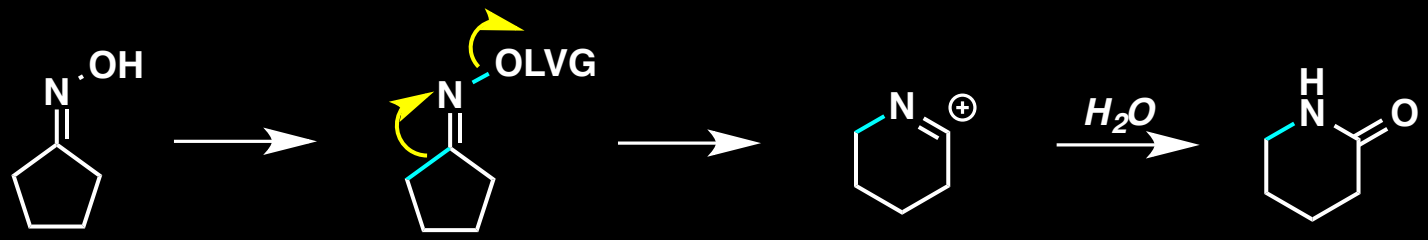
A. P. Marchand, V. S. Kumar, H. K. Hariprakasha, J. Org. Chem. 2001, 66, 2072.
F. W. Demnitz, C. Philippini, R. A. Raphael, J. Org. Chem. 1995, 60, 5114.

The Baeyer-Villager Oxidation/Rearrangement



A. P. Marchand, V. S. Kumar, H. K. Hariprakasha, J. Org. Chem. 2001, 66, 2072.
F. W. Demnitz, C. Philippini, R. A. Raphael, J. Org. Chem. 1995, 60, 5114.

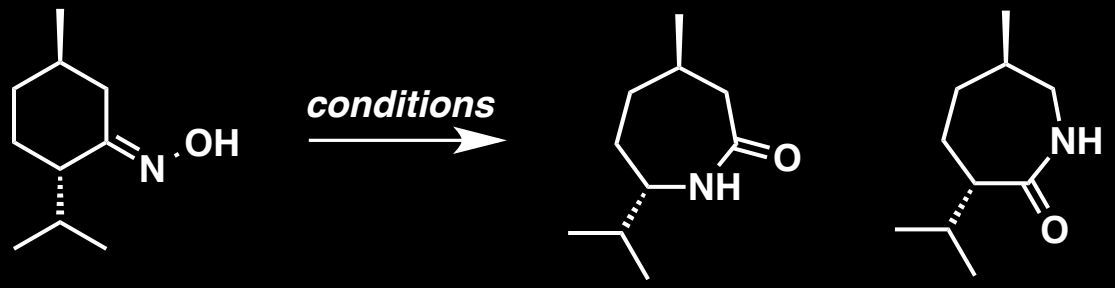
The Beckmann Rearrangement



- *Versatile reaction to make lactams and amides*
- *Prepared starting from hydroxime, with many leaving groups possible*
- *Alkyl group that migrates does so with retention of configuration, and is always anti to the oxime leaving group*

E. Beckmann, Ber. Dtsch. Chem. Ges. 1886, 19, 988.

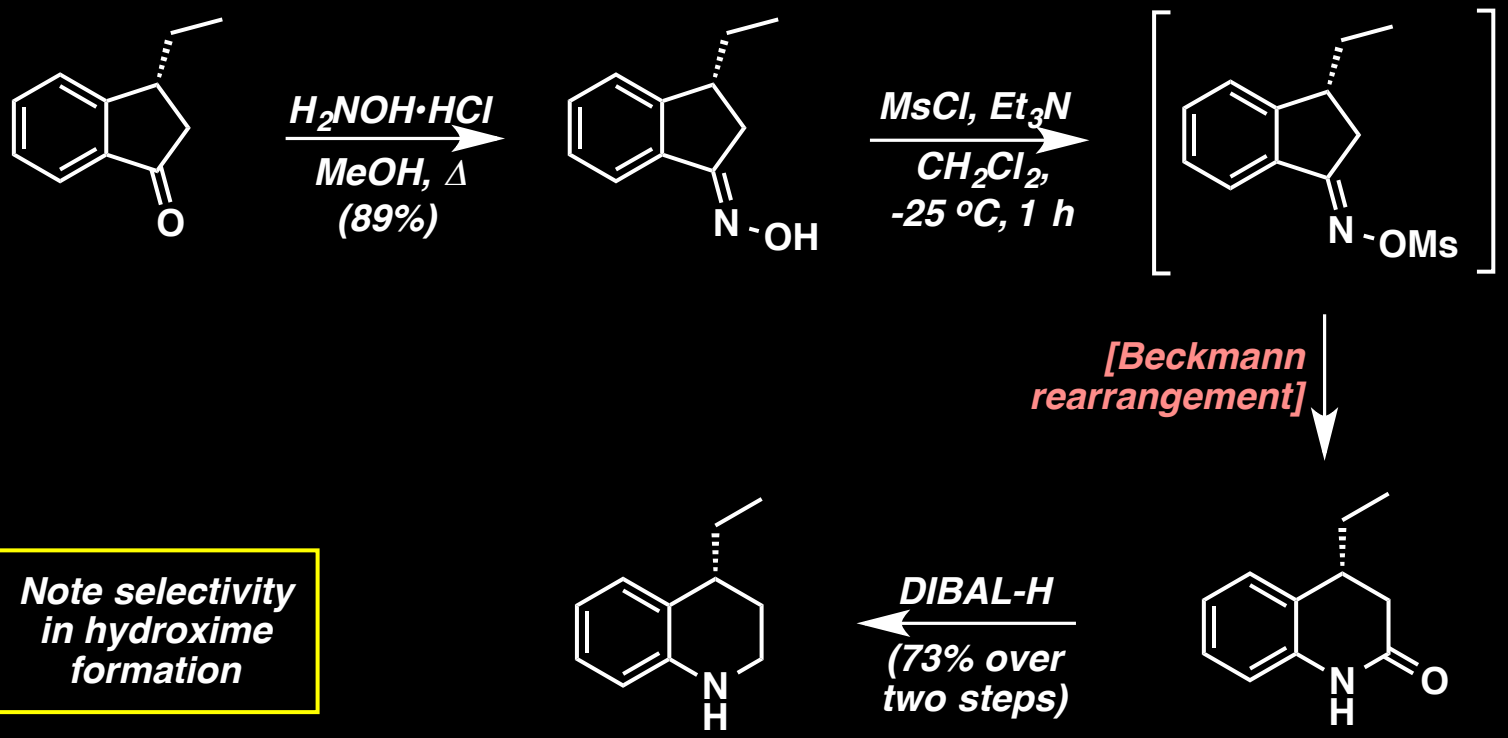
The Beckmann Rearrangement



$POCl_3$, pyridine	98%	2%
$SOCl_2$, pyridine	90%	10%
20% aq. H_2SO_4	43%	57%
HCl/Et_2O	5%	95%

Need to be careful about reaction conditions not isomerizing the oxime derivative to achieve appropriate regiocontrol in the rearrangement

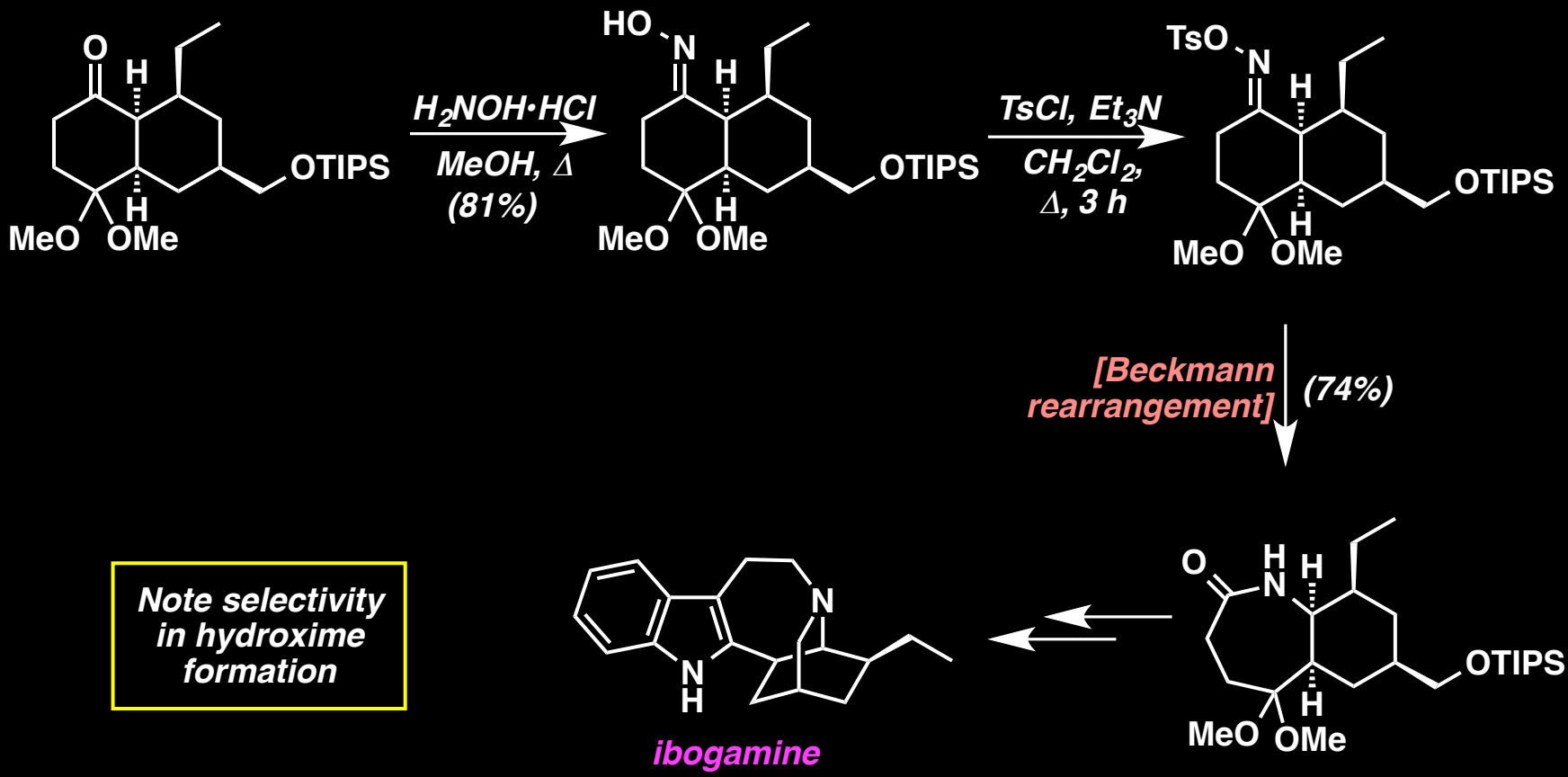
The Beckmann Rearrangement



Note selectivity in hydroxime formation

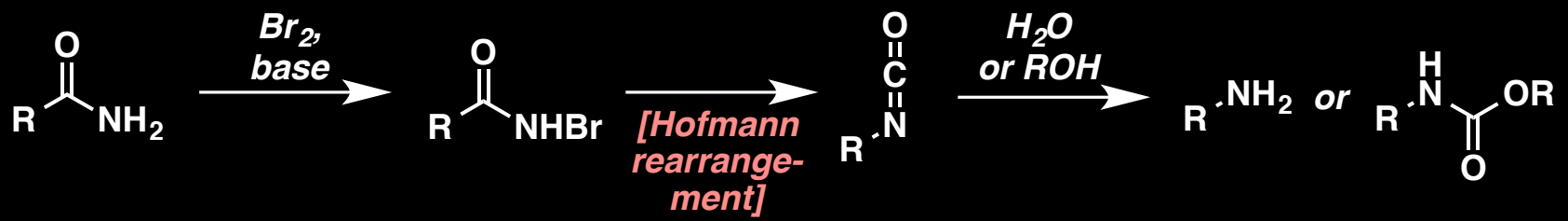
N. S. Mani, M. Wu, Tetrahedron: Asymmetry 2000, 11, 4687.

The Beckmann Rearrangement



J. D. White, Y. Choi, Org. Lett. 2000, 2, 2373.

The Hofmann Rearrangement

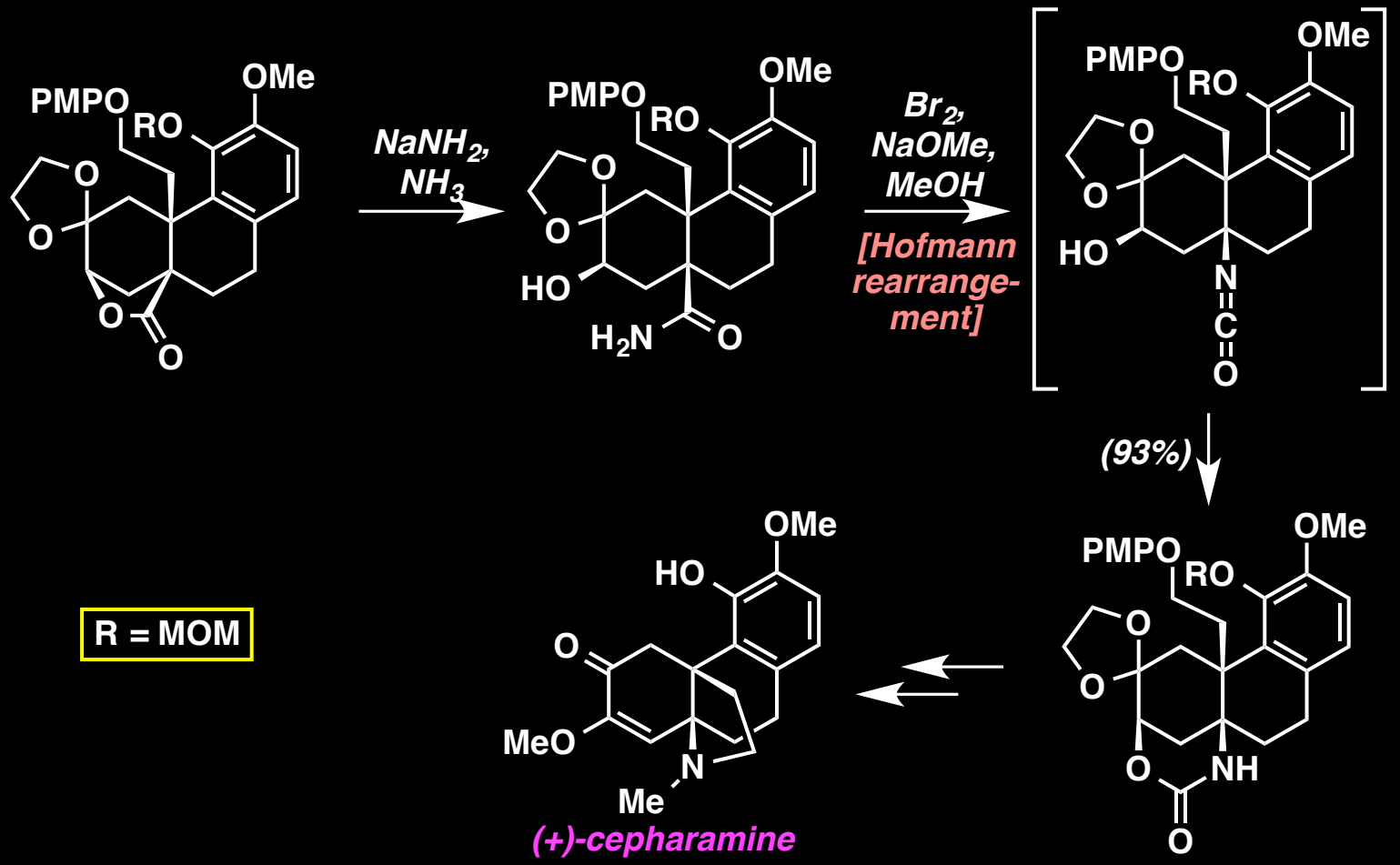


Mechanism:

R group that migrates does so with retention of configuration, and is always anti to the leaving group on nitrogen

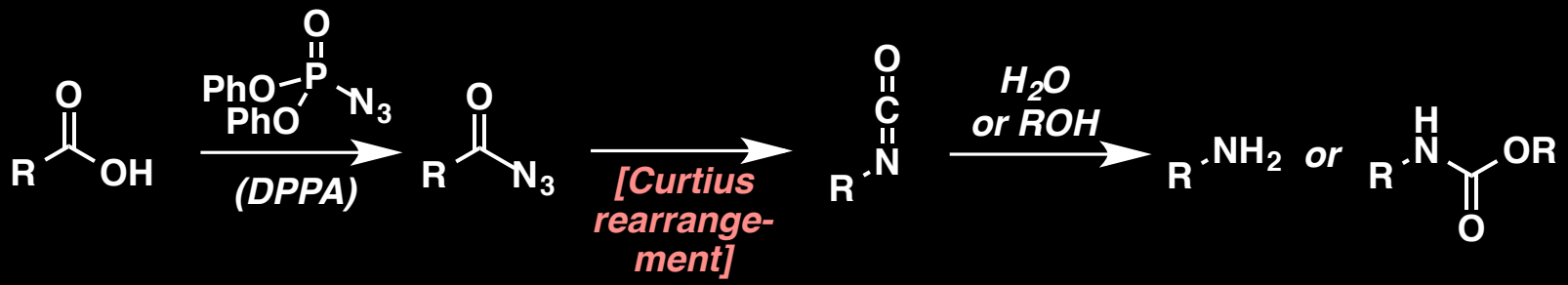
A. W. Hofmann, Ber. 1881, 14, 2725; ibid. 1882, 15, 407, ibid. 1882, 15 762.

The Hofmann Rearrangement



A. G. Schultz, A. Wang, J. Am. Chem. Soc. 1998, 120, 8259.

The Curtius Rearrangement

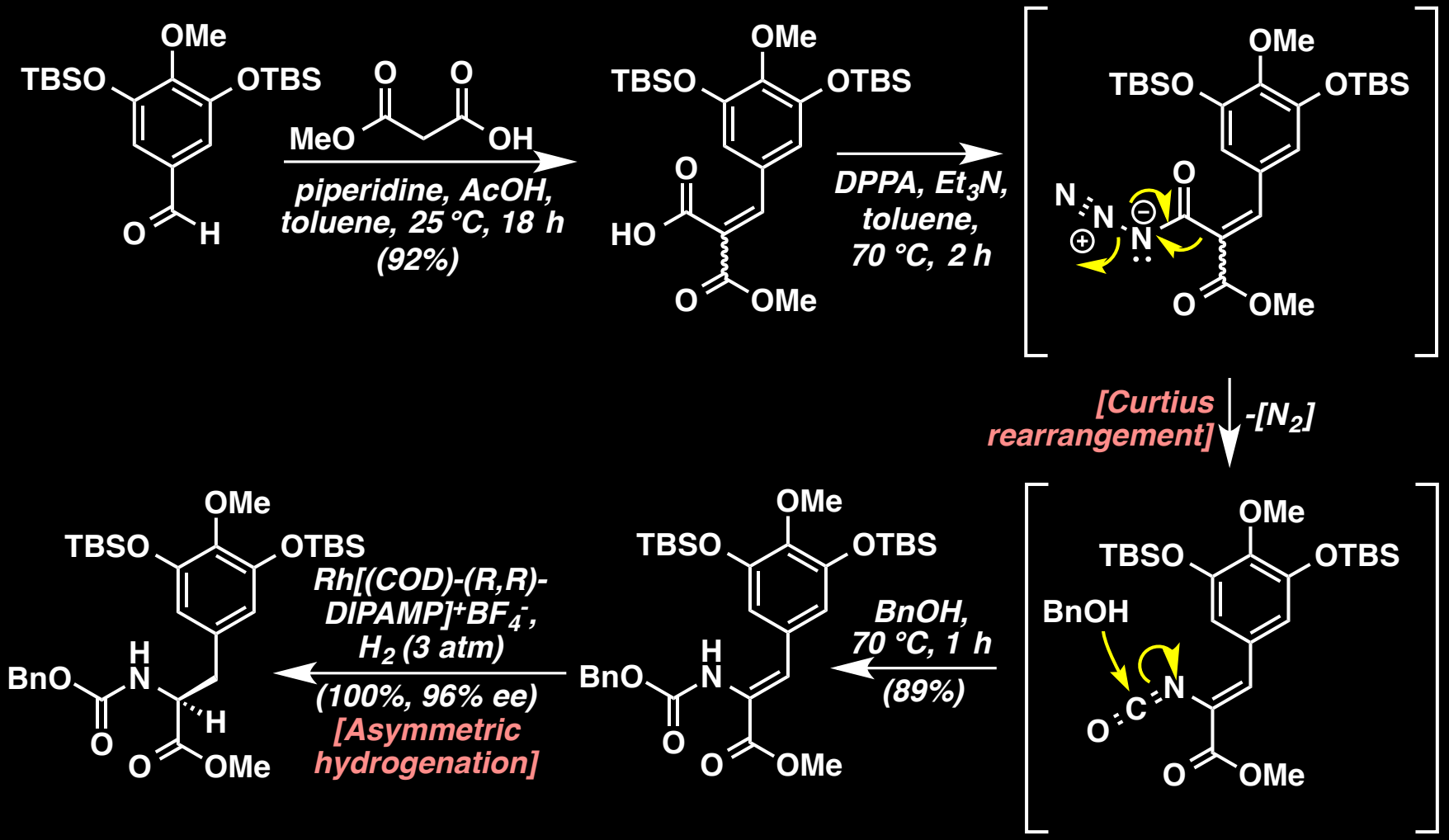


Mechanism:

R group that migrates does so with retention of configuration, and is always anti to the leaving group on nitrogen

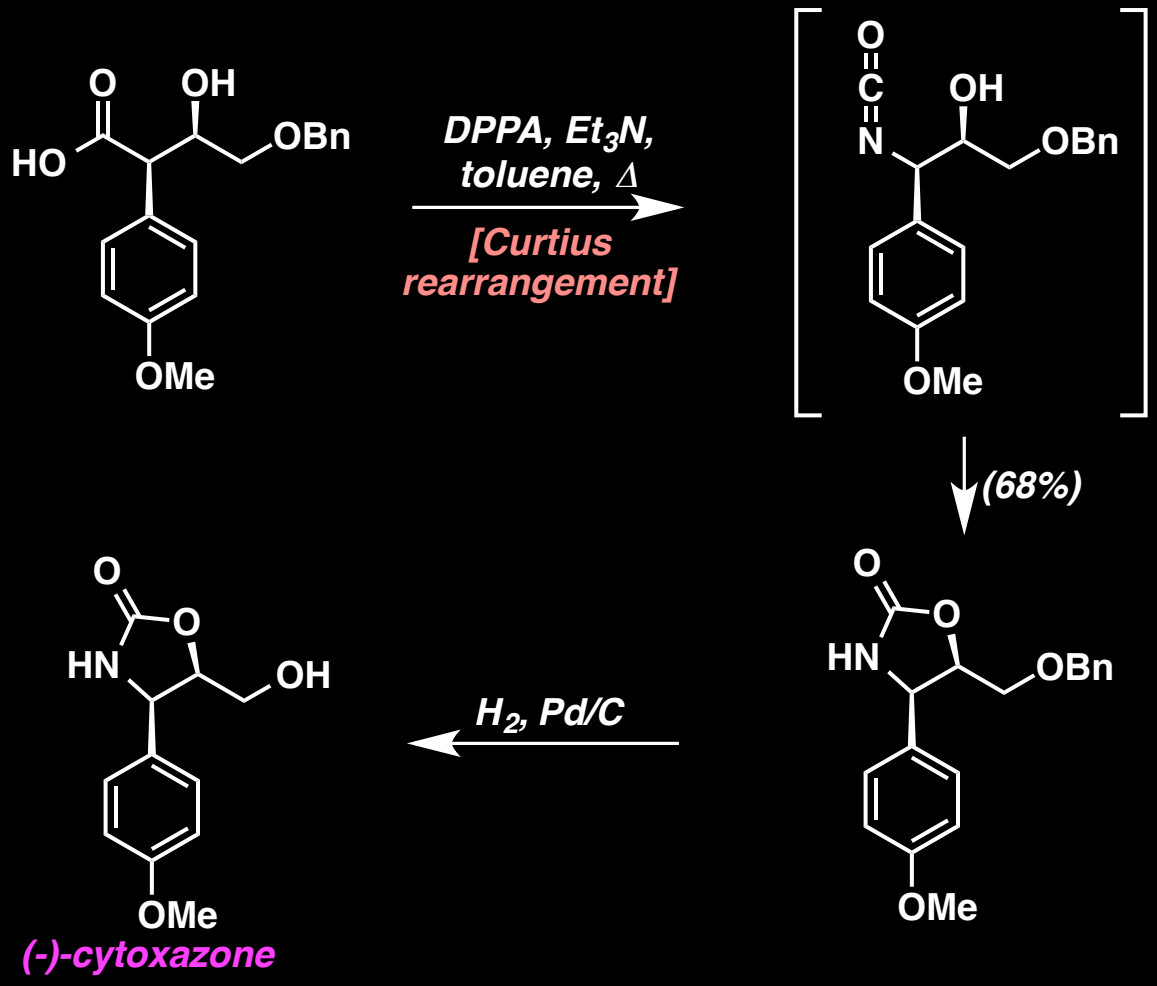
T. Curtius, Ber. 1890, 23, 3023.
T. Curtius, J. Prakt. Chem. 1894, 50, 275.

The Curtius Rearrangement



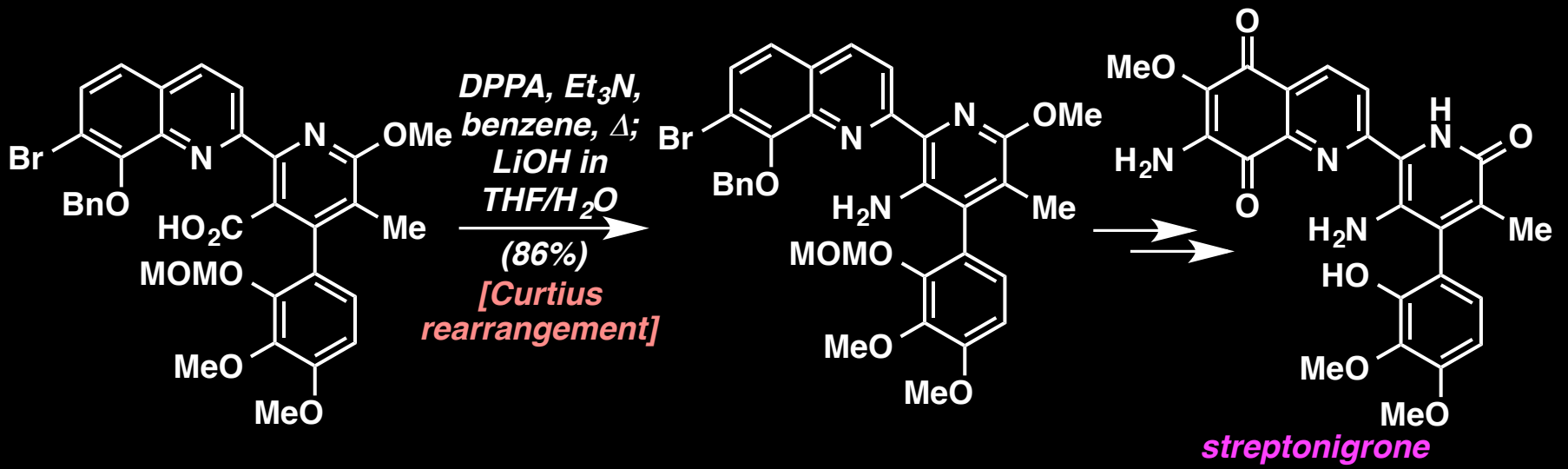
E. J. Corey, D. Y. Gin, R. A. Kania, J. Am. Chem. Soc. 1996, 118, 9202.

The Curtius Rearrangement



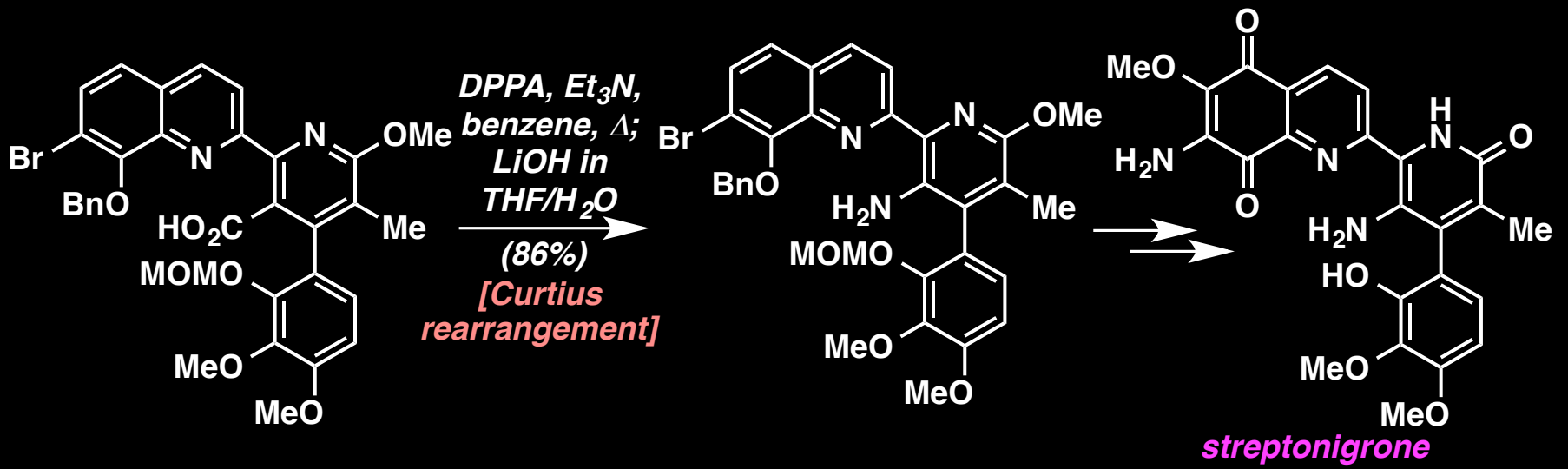
M. Carda, F. Gonzalez, R. Sanchez, J. A. Marco, Tetrahedron: Asymmetry 2002, 13, 1005.

The Curtius Rearrangement



D. L. Boger, K. C. Cassidy, S. Nakahara, J. Am. Chem. Soc. 1993, 115, 10733.
D. L. Boger, S. R. Duff, J. S. Panek, M. Yasuda, J. Org. Chem. 1985, 50, 5789.

The Curtius Rearrangement



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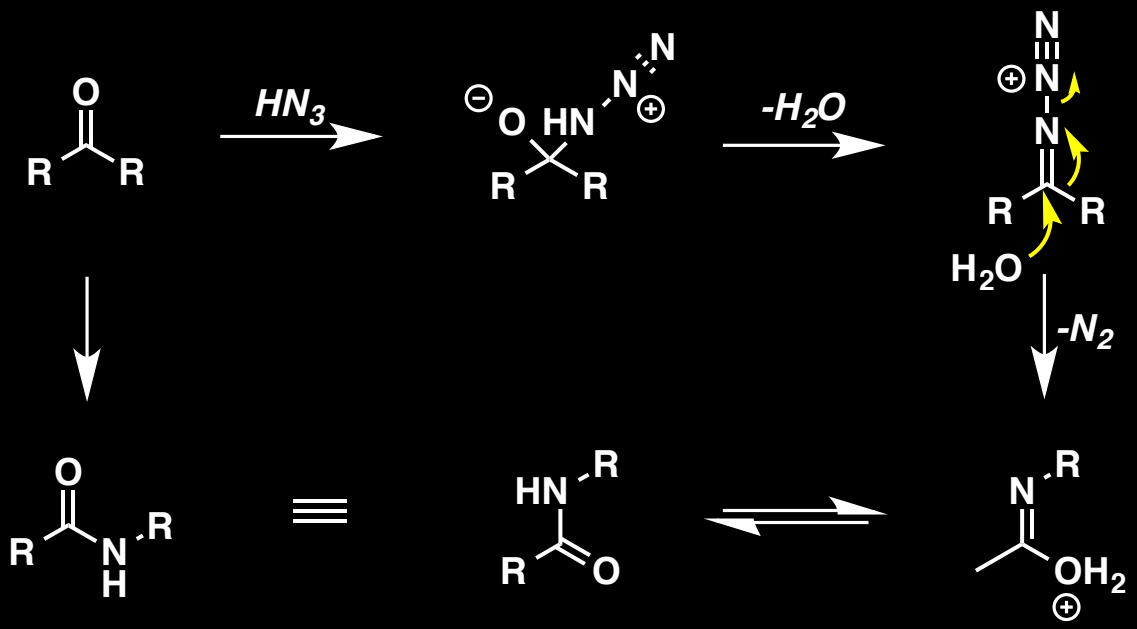
D. L. Boger, S. R. Duff, J. S. Panek, M. Yasuda, J. Org. Chem. 1985, 50, 5789.

The Schmidt Reaction

General name for three individual reactions

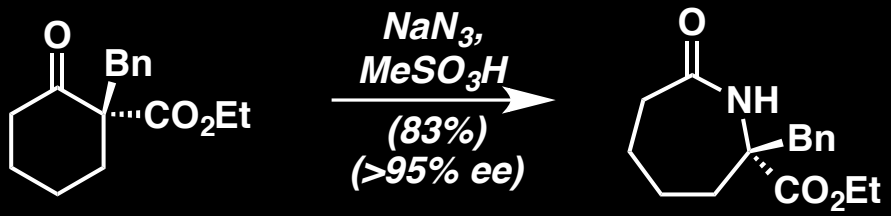
1) Conversion of ketones into amides



Most studied; similar to Beckmann rearrangement with similar migratory aptitude in the vast majority of cases

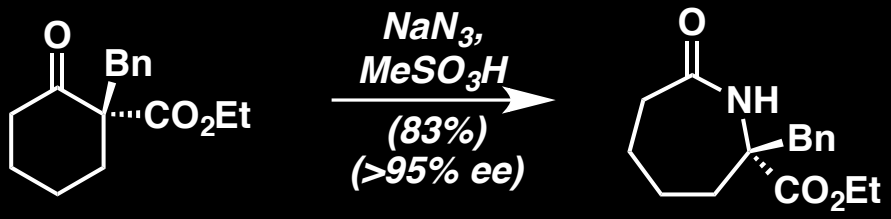
K. F. Schmidt, Angew. Chem. 1923, 36, 511.

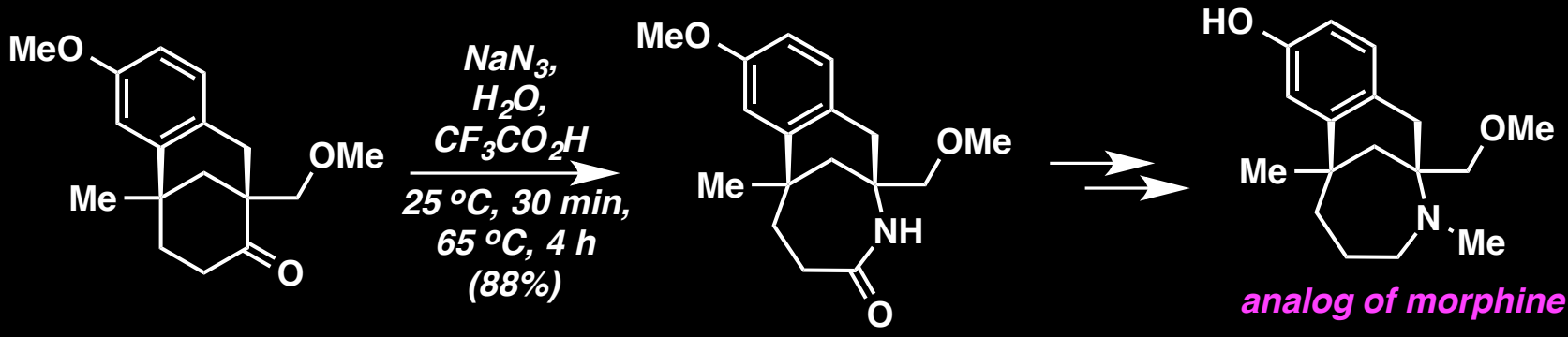
The Schmidt Reaction



G. Georg and co-workers, Bioorg. Med. Chem. Lett. 1991, 1, 125
A. G. Schultz and co-workers, J. Med. Chem. 1996, 39, 1956.
B. T. Smith, J. A. Wendt, J. Aube, Org Lett. 2002, 4, 2577.

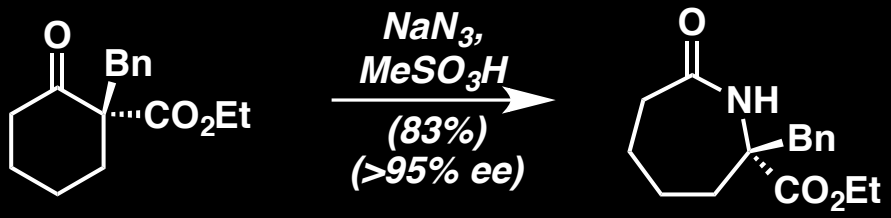
The Schmidt Reaction

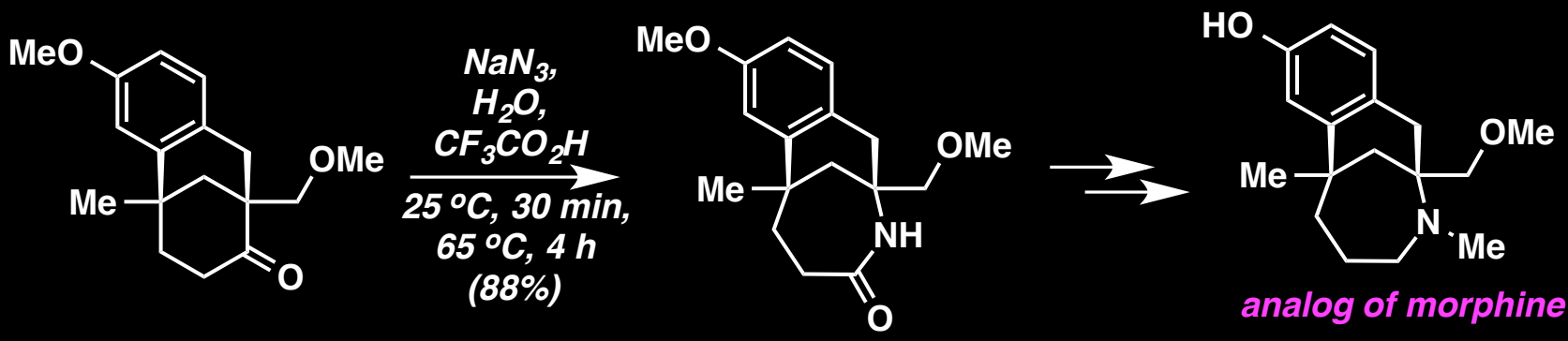


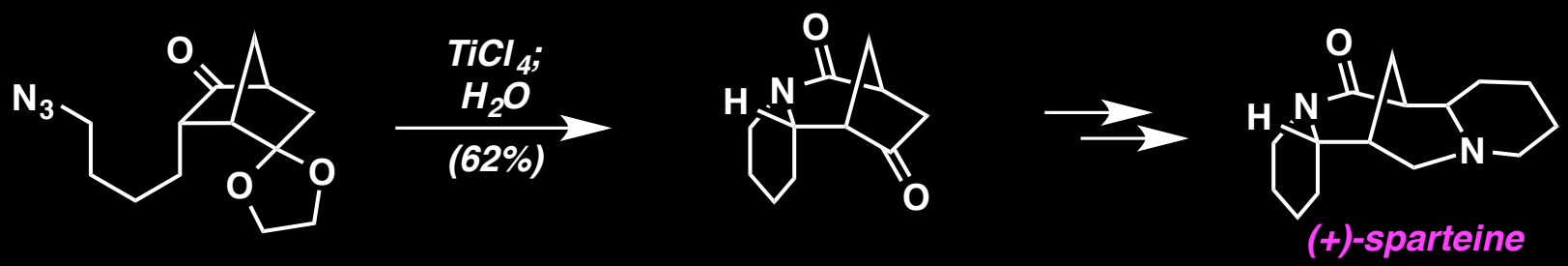


G. Georg and co-workers, Bioorg. Med. Chem. Lett. 1991, 1, 125
A. G. Schultz and co-workers, J. Med. Chem. 1996, 39, 1956.
B. T. Smith, J. A. Wendt, J. Aube, Org Lett. 2002, 4, 2577.

The Schmidt Reaction

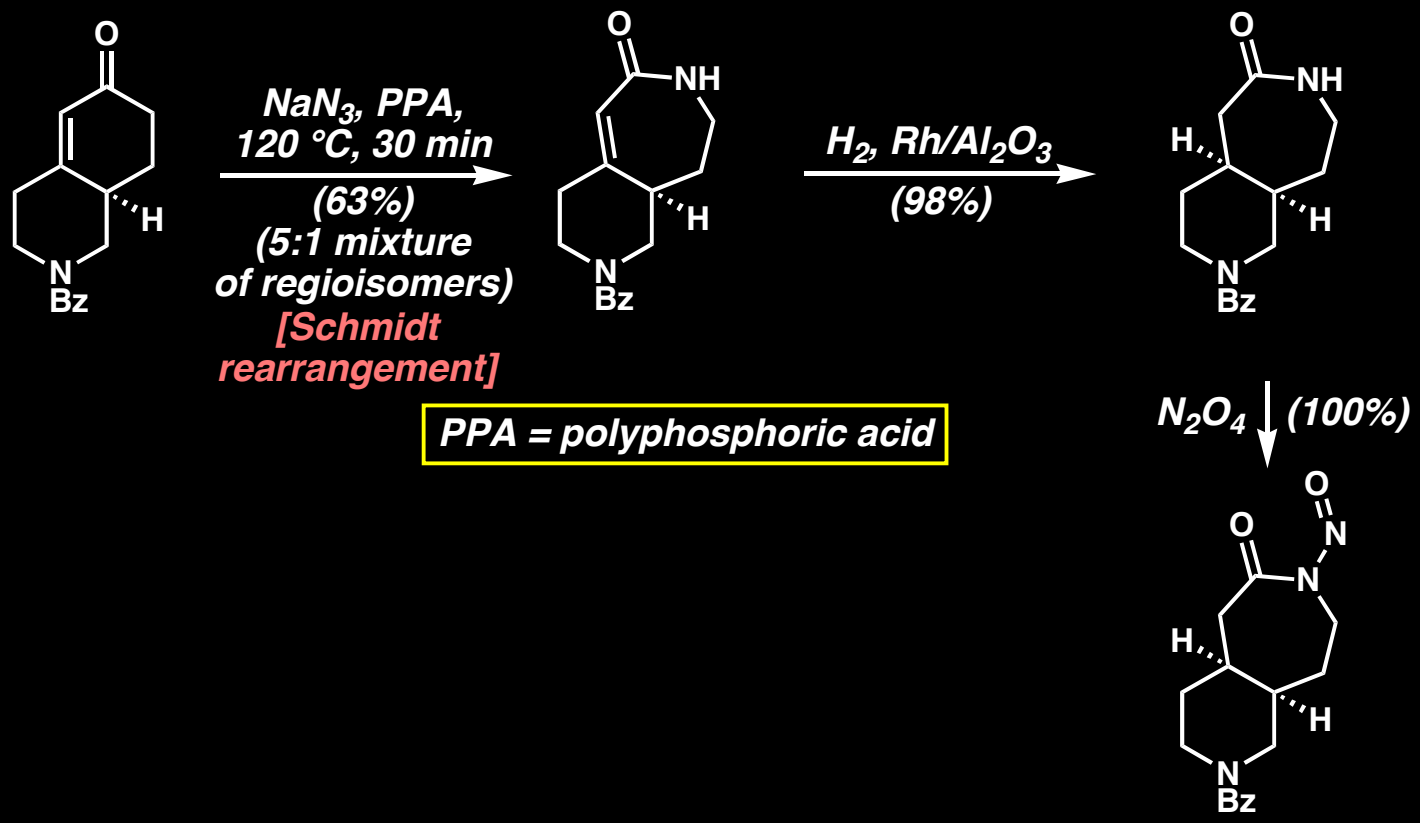






G. Georg and co-workers, Bioorg. Med. Chem. Lett. 1991, 1, 125
A. G. Schultz and co-workers, J. Med. Chem. 1996, 39, 1956.
B. T. Smith, J. A. Wendt, J. Aube, Org Lett. 2002, 4, 2577.

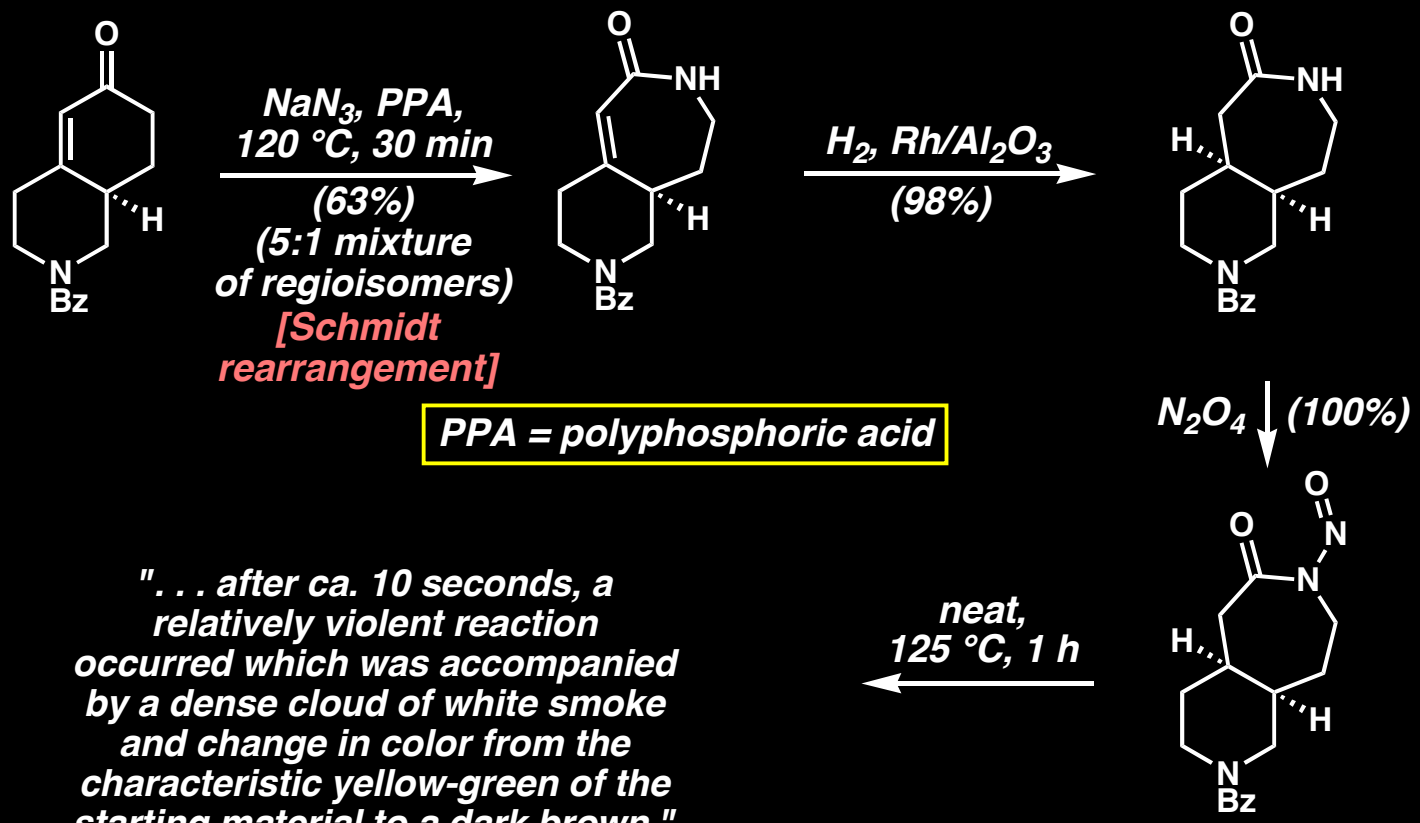
Hoffmann-LaRoche Total Syntheses of Quinine (1970s)



PPA = polyphosphoric acid

M.R. Uskokovic and co-workers, J. Am. Chem. Soc. 1978, 100, 581 and 589
and references cited therein

Hoffmann-LaRoche Total Syntheses of Quinine (1970s)

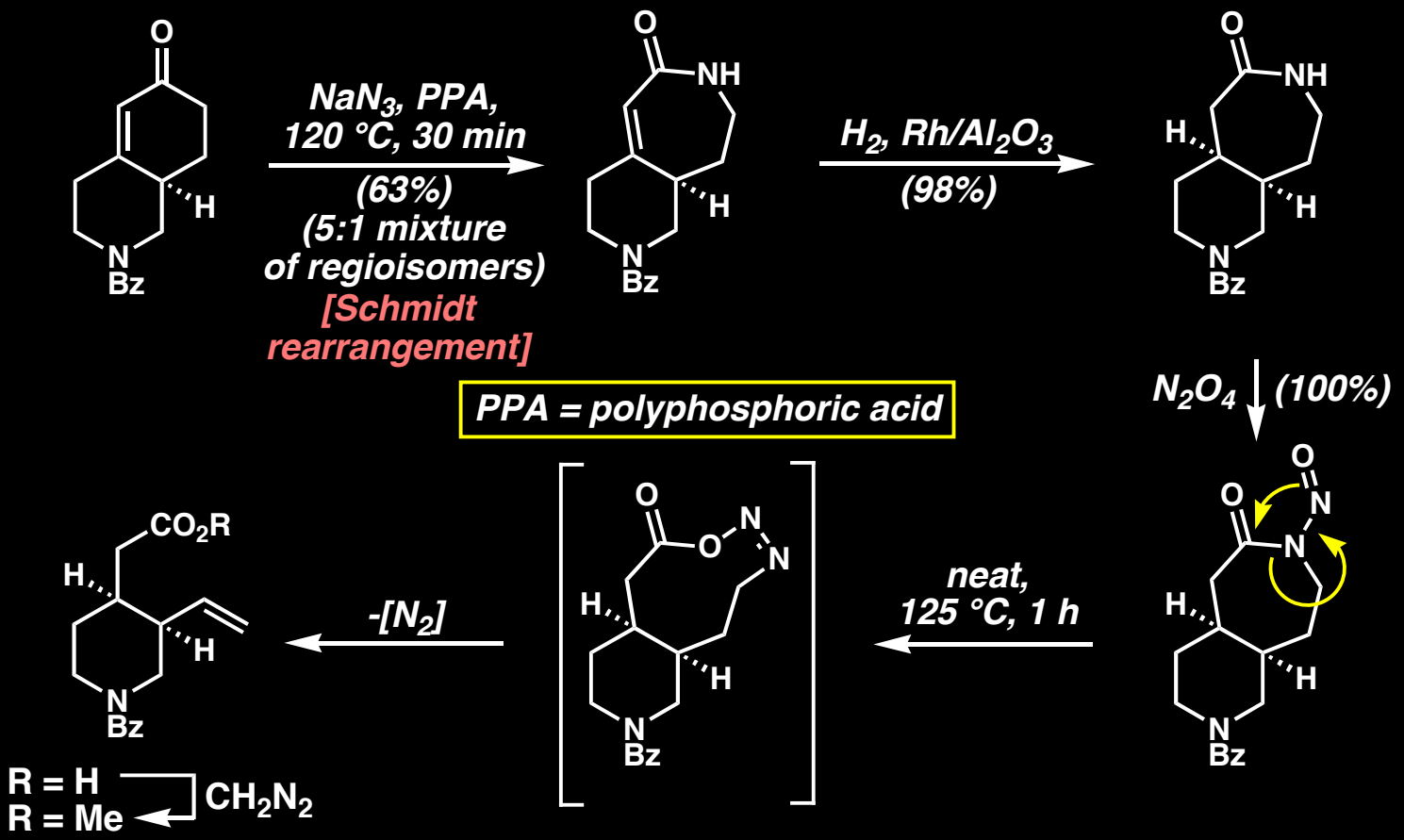


PPA = polyphosphoric acid

". . . after ca. 10 seconds, a relatively violent reaction occurred which was accompanied by a dense cloud of white smoke and change in color from the characteristic yellow-green of the starting material to a dark brown."

M.R. Uskokovic and co-workers, J. Am. Chem. Soc. 1978, 100, 581 and 589 and references cited therein

Hoffmann-LaRoche Total Syntheses of Quinine (1970s)

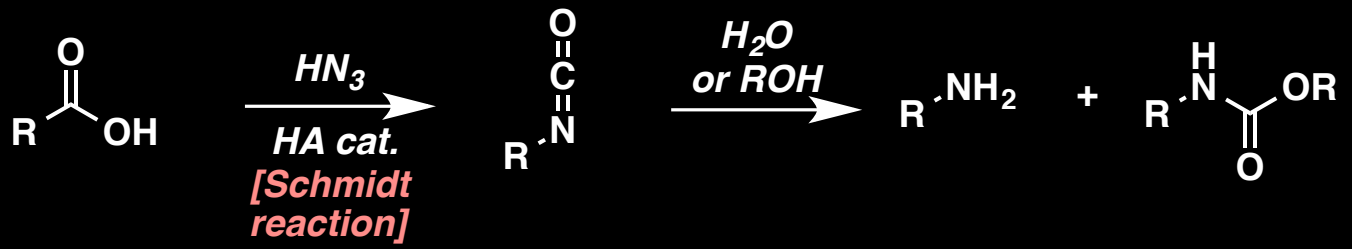


M.R. Uskokovic and co-workers, J. Am. Chem. Soc. 1978, 100, 581 and 589
and references cited therein

The Schmidt Reaction

General name for three individual reactions

2) Conversion of carboxylic acids into amines



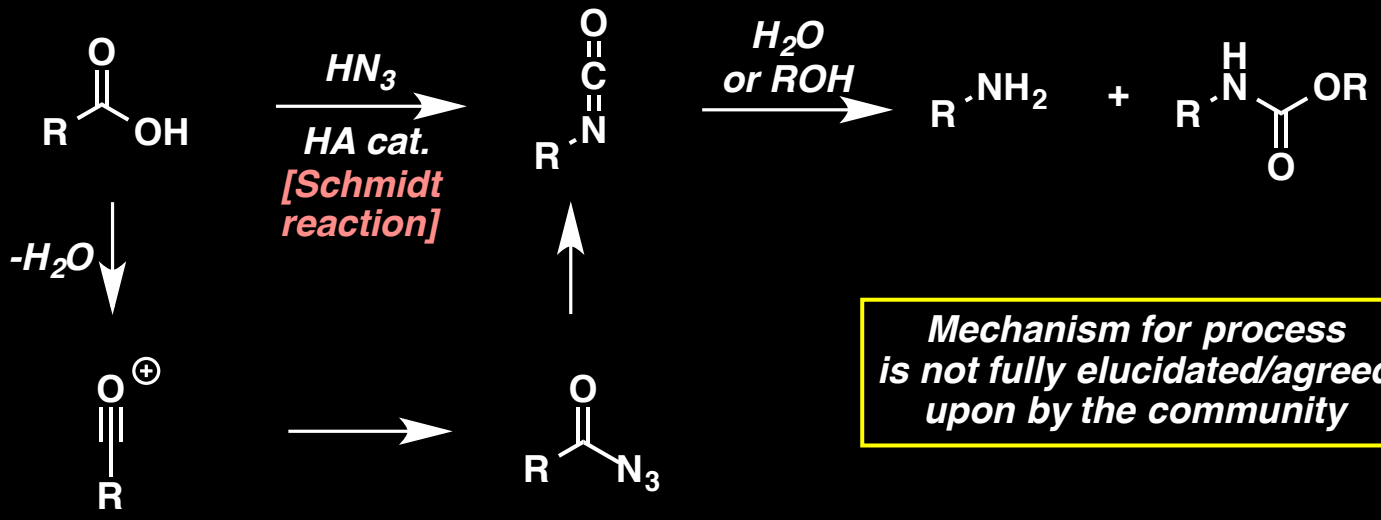
Acid catalyst usually is H_2SO_4, PPA, TFA/TFAA, or a Lewis acid
Especially good for cases where R is hindered
Harsher conditions than Curtius/Hofmann rearrangements, but done in fewer steps

K. F. Schmidt, Angew. Chem. 1923, 36, 511.

The Schmidt Reaction

General name for three individual reactions

2) Conversion of carboxylic acids into amines



Mechanism for process is not fully elucidated/agreed upon by the community

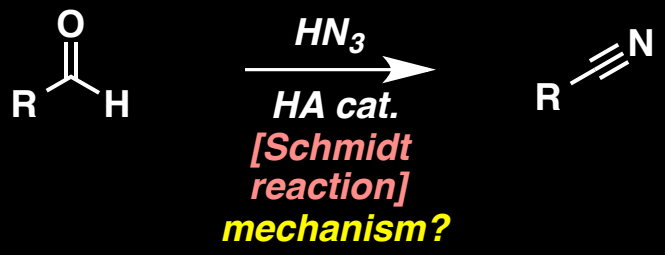
Acid catalyst usually is H_2SO_4, PPA, TFA/TFAA, or a Lewis acid
Especially good for cases where R is hindered
Harsher conditions than Curtius/Hofmann rearrangements, but done in fewer steps

K. F. Schmidt, Angew. Chem. 1923, 36, 511.

The Schmidt Reaction

General name for three individual reactions

3) Conversion of aldehydes into nitriles

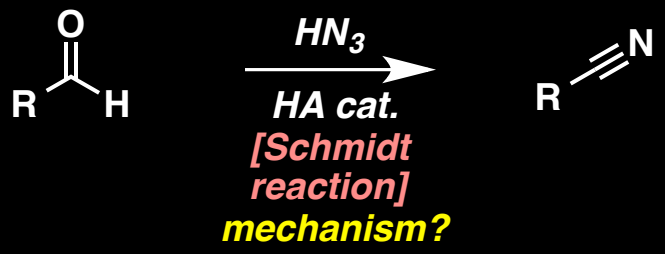


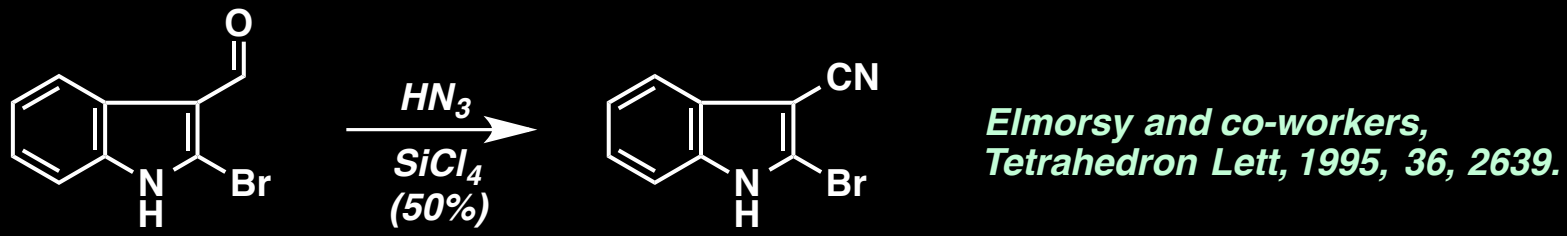
K. F. Schmidt, Angew. Chem. 1923, 36, 511.

The Schmidt Reaction

General name for three individual reactions

3) Conversion of aldehydes into nitriles





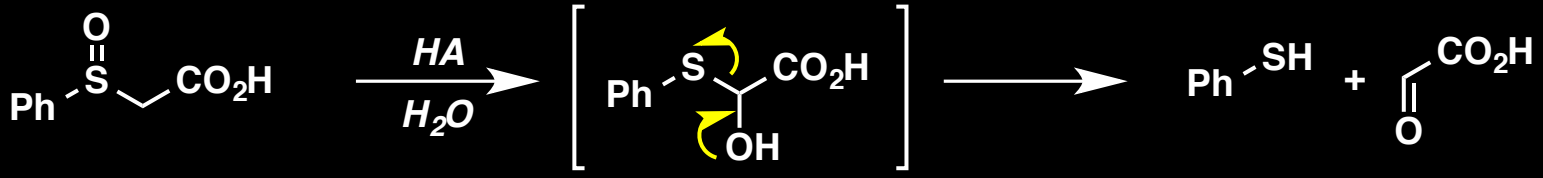
Elmorsy and co-workers, Tetrahedron Lett, 1995, 36, 2639.

Particularly effective for aromatic aldehydes
Schmidt rearrangement is the usual by-product
What would be a more common, two step way to do the same thing?

K. F. Schmidt, Angew. Chem. 1923, 36, 511.

The Pummerer Rearrangement

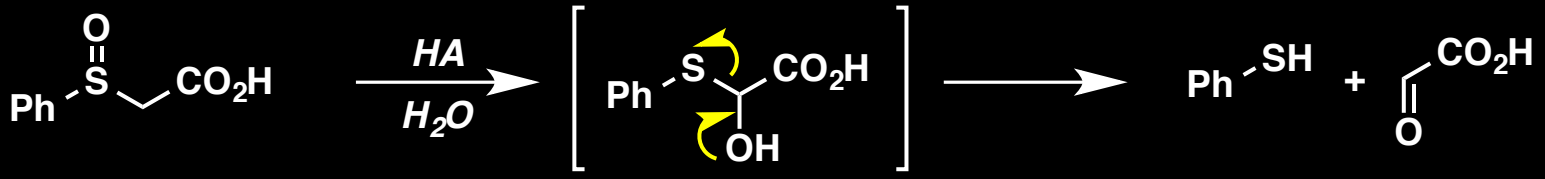
Original discovery (1909)



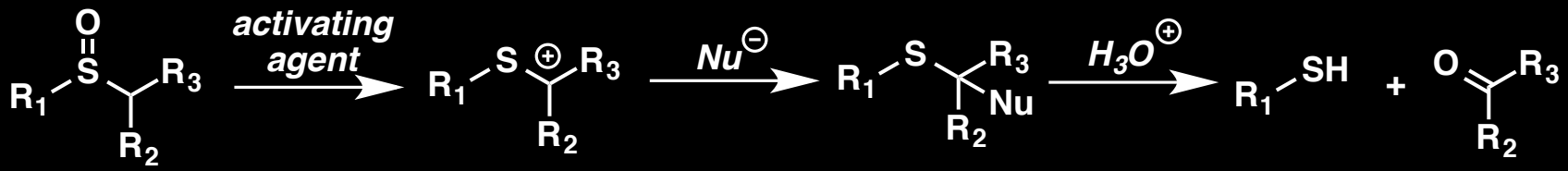
R. Pummerer, Ber. 1909, 42, 2282.
For a review, see: A. Padwa, D. E. Gunn, M. H. Osterhout, Synthesis 1997, 1353.

The Pummerer Rearrangement

Original discovery (1909)



Pummerer Rearrangement (Modern version)



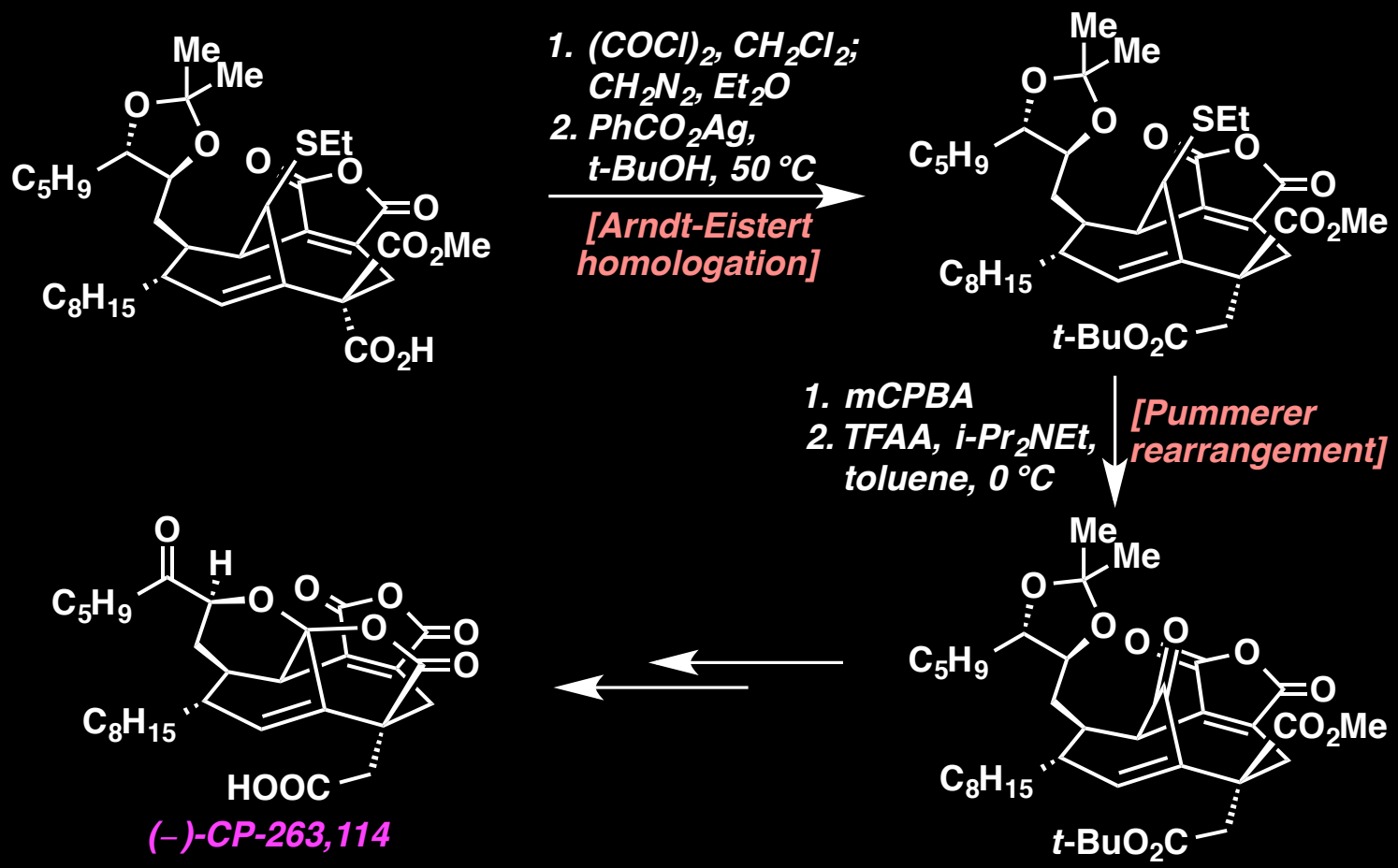
Activating agents: *HCl, H_2SO_4, Ac_2O, TFAA, TMSX, PCl_3, $Sn(OTf)_2$*
Nucleophile: *OH, OR, OAr, acids, halogens, thiols, amines*

R. Pummerer, Ber. 1909, 42, 2282.
For a review, see: A. Padwa, D. E. Gunn, M. H. Osterhout, Synthesis 1997, 1353.

The Pummerer Rearrangement

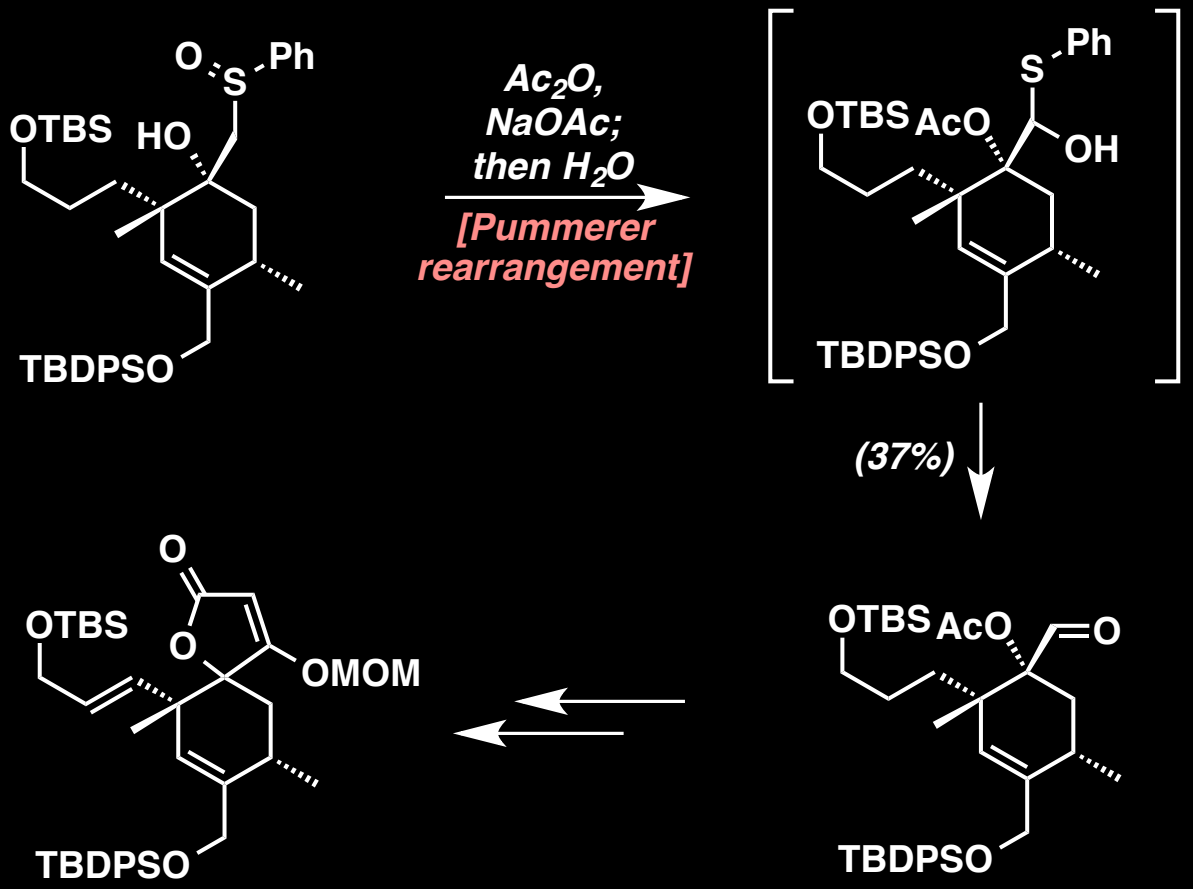
Mechanism:

The Pummerer Rearrangement



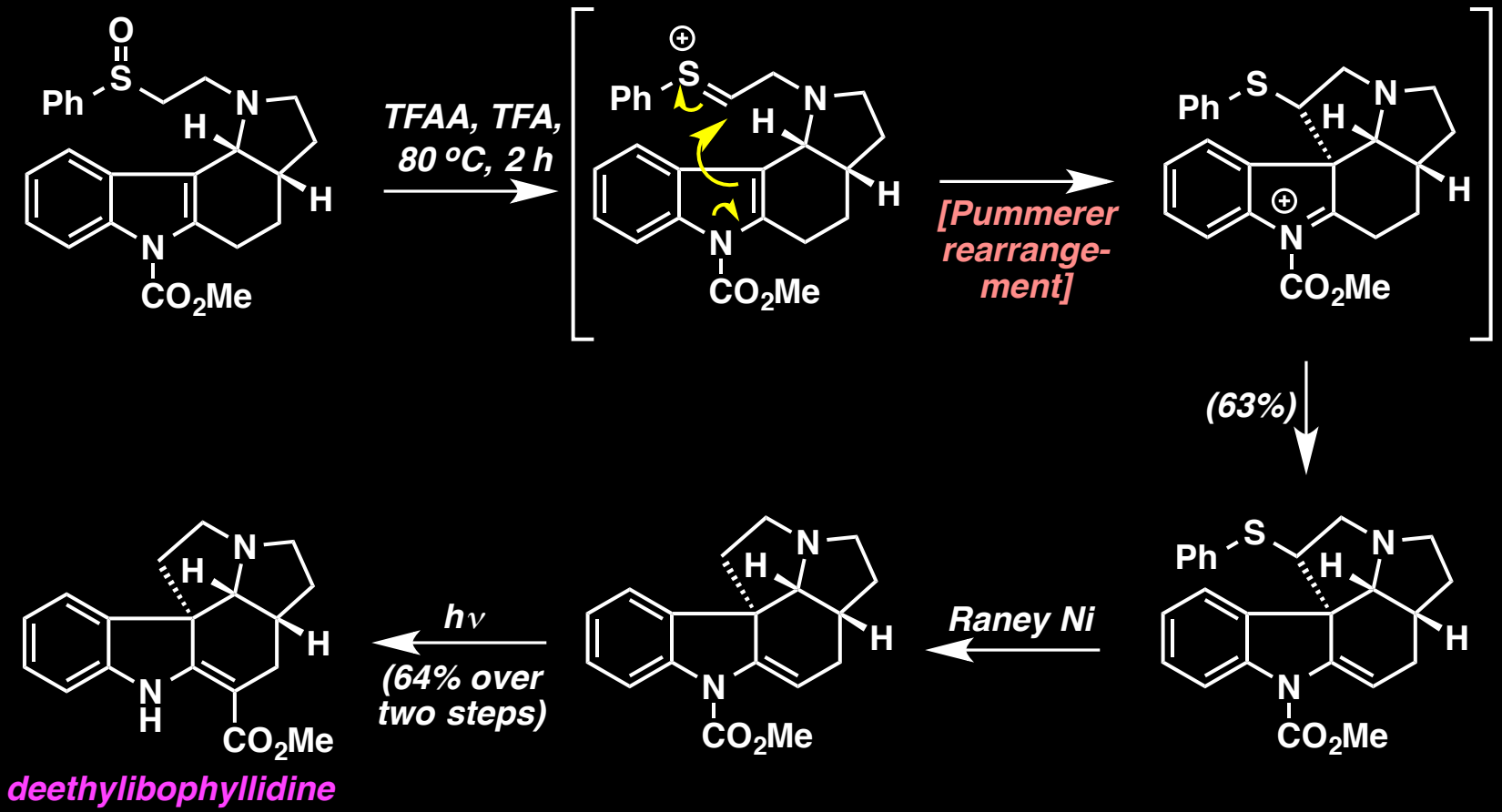
N. Waizumi, T. Itoh, T. Fukuyama, J. Am. Chem. Soc. 2000, 122, 7825.

The Pummerer Rearrangement



W. R. Roush, C. Limberakis, R. K. Kunz, D. A. Barda, Org. Lett. 2002, 4, 1543.

The Pummerer Rearrangement



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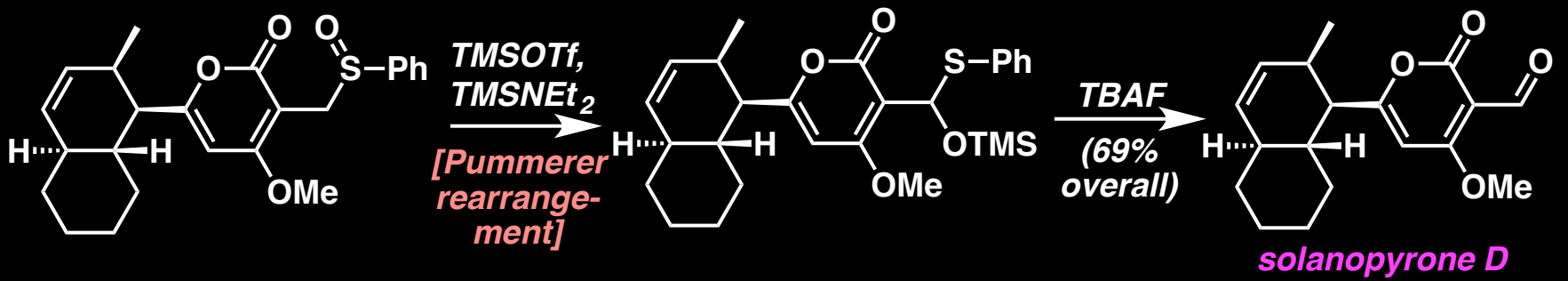
The Pummerer Rearrangement



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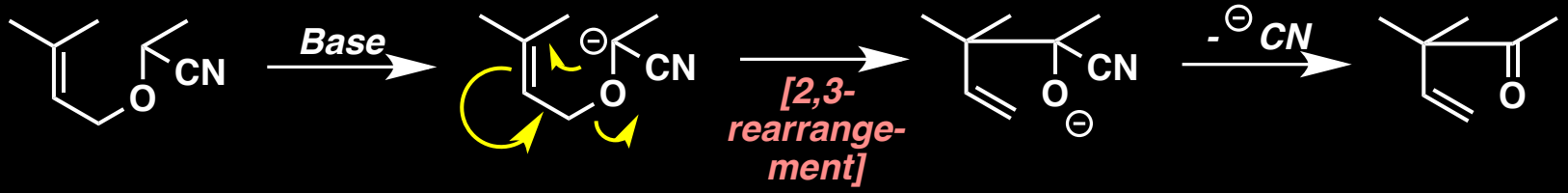

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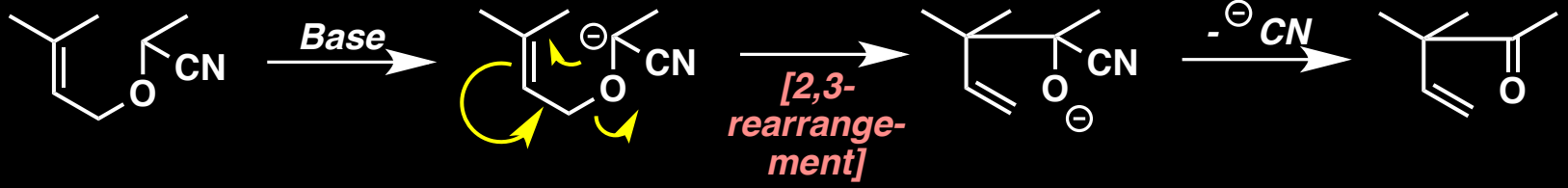

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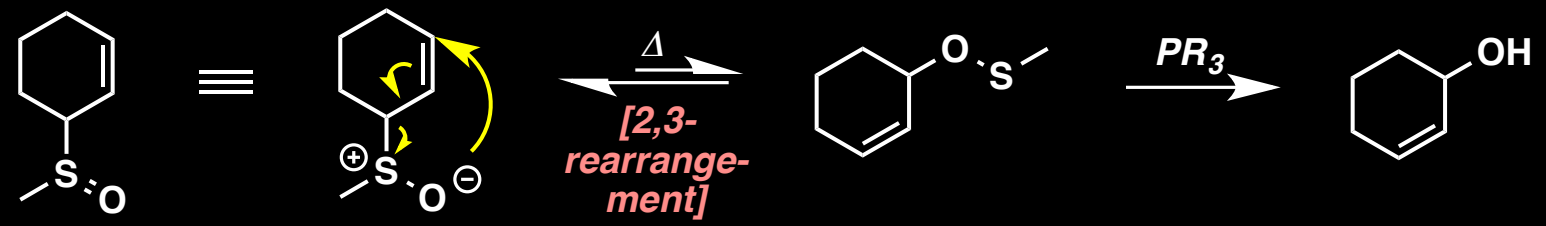

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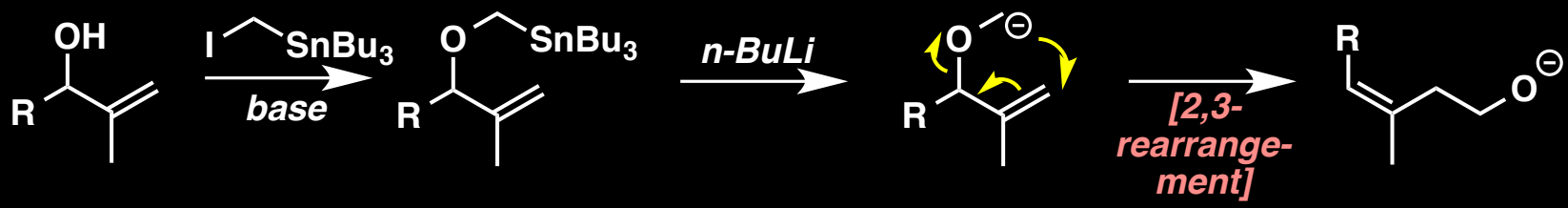

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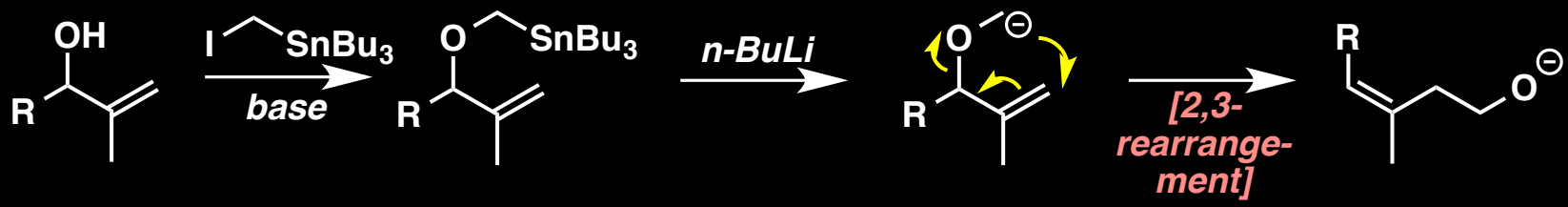

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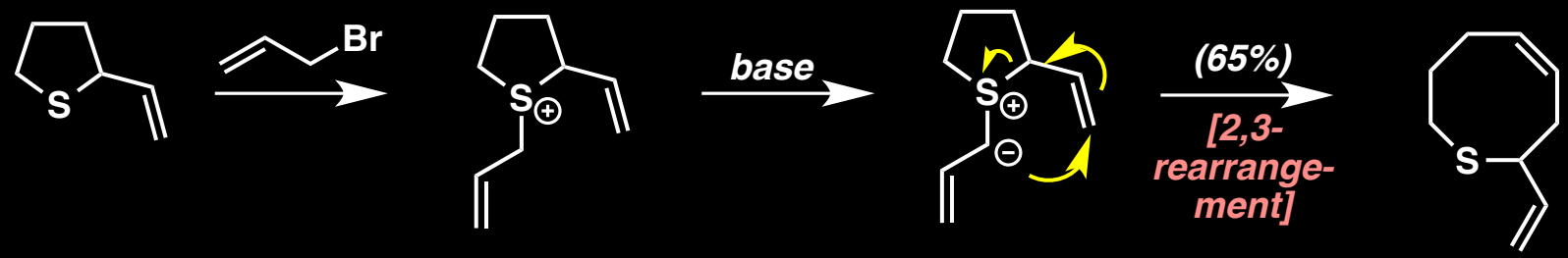
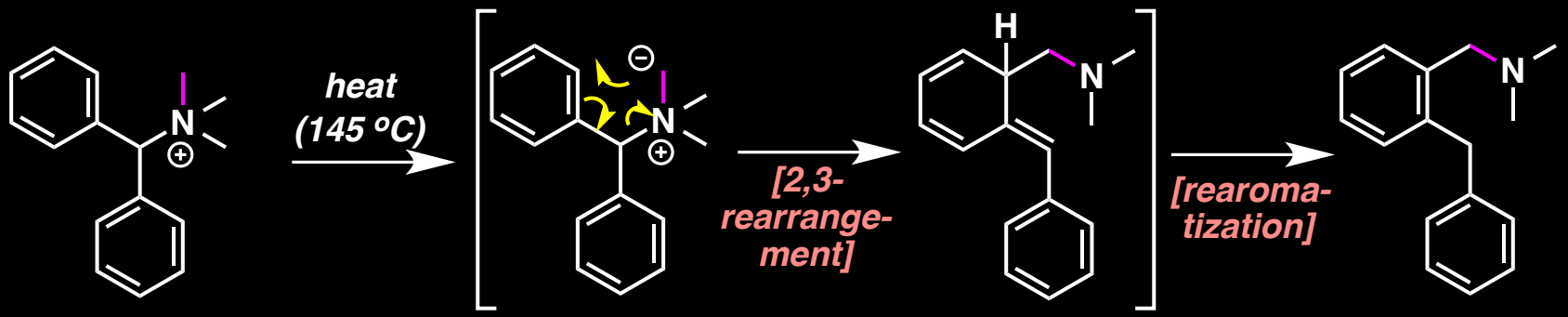


The Sommelet-Hauser Rearrangement

Sommelet (1937)



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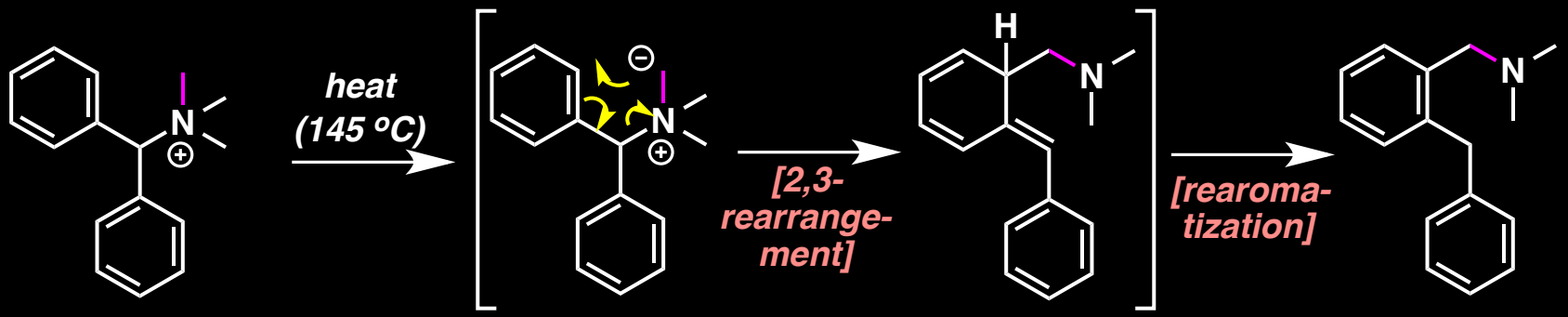
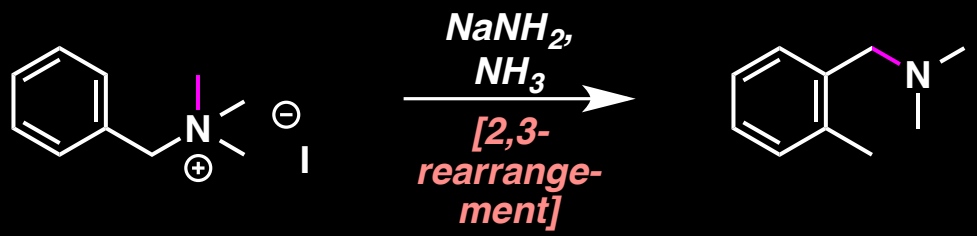
Sommelet (1937)



Hauser (1951)



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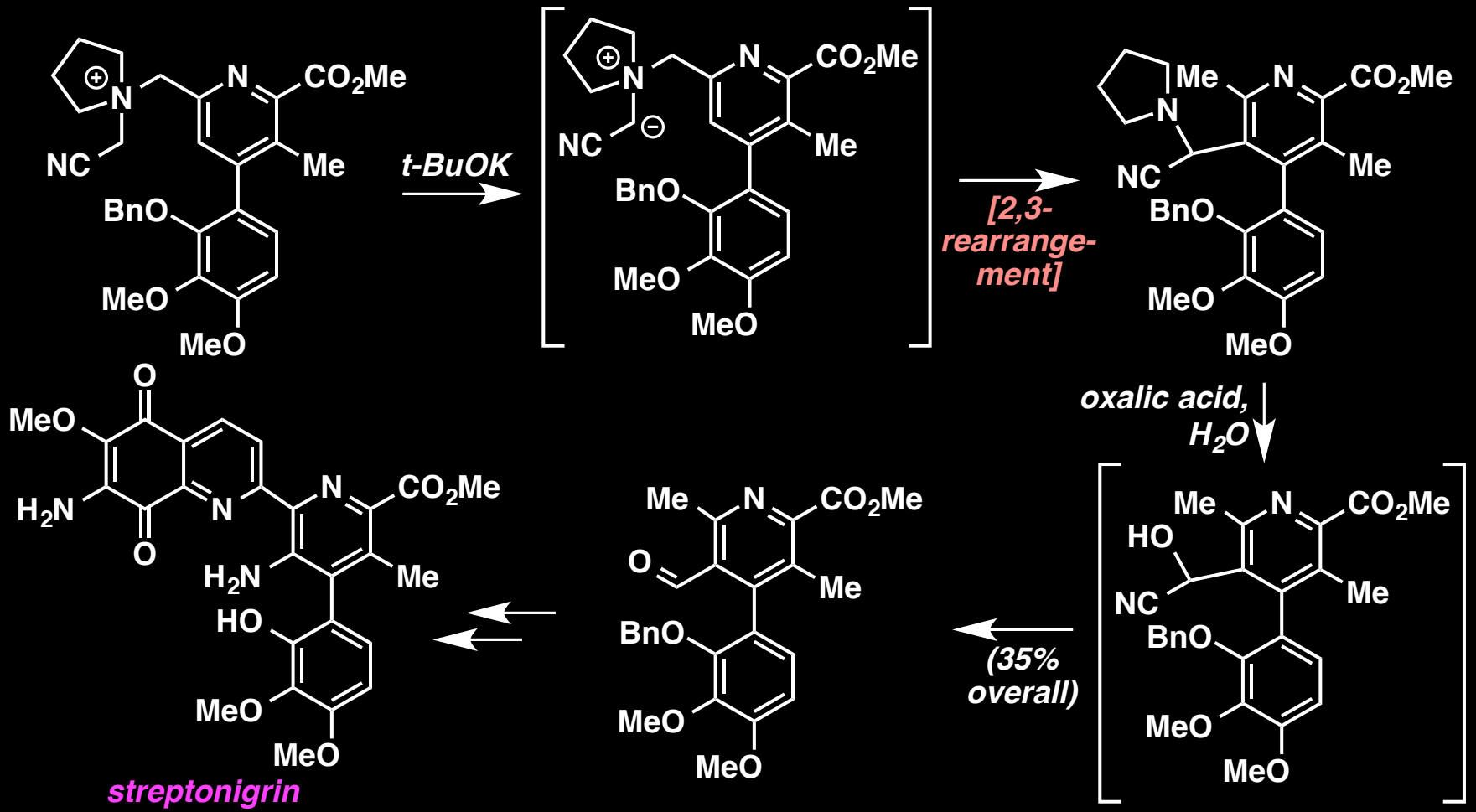

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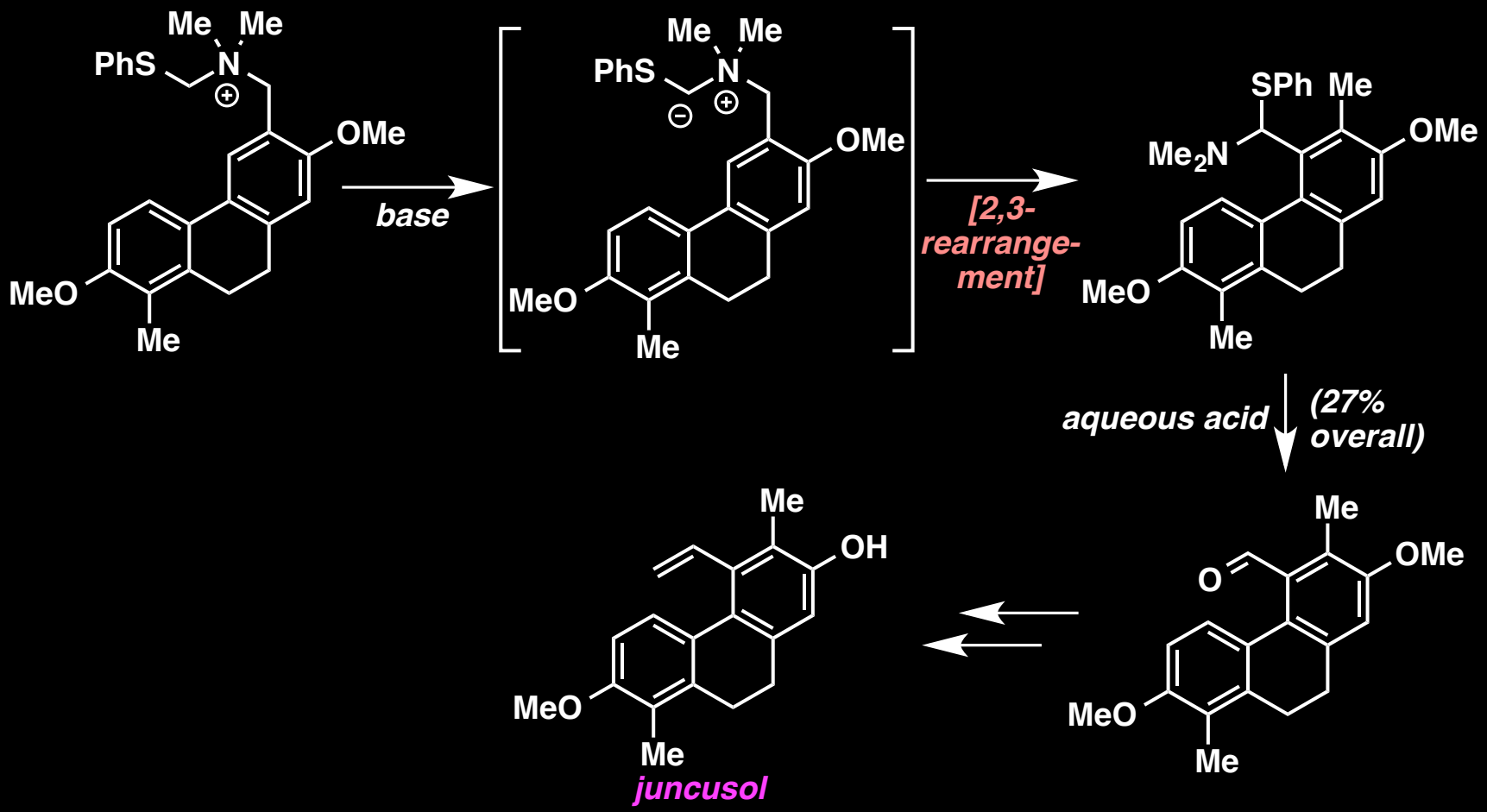

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